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Arginine-rich self-assembling peptides as potent antibacterial gels

Ana Salomé Veiga [a,b], Chomdao Sinthuvanich [a,c], Diana Gaspar [b], Henri G. Franquelim [b], Miguel A.R.B. Castanho [b], Joel P. Schneider [a,*]

[a] Chemical Biology Lab, National Cancer Institute, Frederick, MD 21702, USA
[b] Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisbon, Portugal
[c] Chemistry and Biochemistry Department, University of Delaware, Newark, DE 19716, USA

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ABSTRACT

Hydrogel materials that display inherent activity against bacteria can be used to directly treat accessible wounds to prevent or kill existing infection. Hydrogels composed of self-assembling β-hairpin peptides, having a high content of arginine, were found to be extremely effective at killing both gram-positive and gram-negative bacteria, including multi-drug resistant *Pseudomonas aeruginosa*. No added antibacterial agents are necessary to realize activity. Using self-assembling peptides for material construction allows facile structure–activity relationships to be determined since changes in peptide sequence at the monomer level are directly transposed to the bulk material's antibacterial properties. SAR studies show that arginine content largely influences the hydrogel's antibacterial activity, and influences their bulk rheological properties. These studies culminated in an optimized gel, composed of the peptide PEP6R (VKVRVRVRV^{D}PPTRVRVRVKV). PEP6R gels prepared at 1.5 wt % or higher concentration, demonstrate high potency against bacteria, but are cytocompatible toward human erythrocytes as well as mammalian mesenchymal stem cells. Rheological studies indicate that the gel is moderately stiff and displays shear-thin recovery behavior, allowing its delivery via simple syringe.

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1. Introduction

Bacterial infections are a common problem associated with dermal wounds [1,2]. These infections can prolong or impair wound healing, contributing to tissue morbidity and in extreme cases, result in sepsis. *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) belong to a suite of bacteria commonly found in nosocomial infections [3,4]. *P. aeruginosa* is an especially bad actor, being the fourth most common nosocomial pathogen accounting for 10% of all hospital infections. *P. aeruginosa* infection remains a serious problem for patients hospitalized for cancer, AIDS, burns and cystic fibrosis [5–8].

Antibacterial hydrogels can be used to directly treat accessible wounds to prevent or kill existing infection. Hydrogels can be used to deliver small molecule antibiotics or the material, itself, can be designed to be the antibacterial agent, circumventing the need to encapsulate therapeutic [9–11]. For many material types, including gels, their surfaces can be endowed with antibacterial properties. This is typically accomplished by covalently immobilizing known antibiotics or fixing silver nanoparticles or quaternary ammonium groups to their surfaces [12–16]. Materials that inherently display polycationic surfaces are also known to be active against a broad spectrum of both Gram-positive and Gram-negative bacteria via a direct-contact mechanism involving bacterial membrane disruption [10].

We have shown that antibacterial hydrogels can be prepared from lysine-rich, self-assembling β-hairpin peptides. These peptides assemble into a polycationic fibrillar network capable of killing bacteria via a mechanism involving membrane disruption. When bacteria come in contact with the fibril surface, their membranes become comprised and this leads to cell death by lysis. An excellent feature of these materials is that the surface chemistry of their fibrillar networks can be varied by simply modulating the amino acid composition of the peptide monomer used for self-assembly [17,18]. This allows one to modify the structure of these gels at the nanometer length scale in efforts to create new materials with enhanced activity.

An excellent source of inspiration for the design of new, more effective materials is Nature. Antimicrobial peptides (AMPs) are a ubiquitous class of host defense molecules used across species. AMPs are small, water-soluble peptides that fold into amphiphilic conformations, typically helices and β-sheets, which display opposing hydrophobic and polycationic surfaces. The cationic face of an AMP is responsible for engaging the negatively charged, phospho-rich surface of the bacteria's membrane via hydrogen bonding and electrostatic interactions. Once bound to the outer-

* Corresponding author.
E-mail addresses: joel.schneider@nih.gov, schneiderjp@mail.nih.gov (J.P. Schneider).

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